EXPERT SYSTEMS IN PHARMACEUTICAL PRODUCT DEVELOPMENT

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INTRODUCTION

The process of formulation, whether it be for oral products (e.g., tablets and capsules), parenterals [e.g., intravenous (iv) injections], or any one of the myriad of pharmaceutical products, is generically the same. The process begins with some form of product specification and ends with the generation of one or more formulations that meet the requirements. Although the formulation consists of a list of ingredients and their proportions together with some processing variables where appropriate, the specification can vary considerably from one application to another. In some cases it may be very specific, expressed in terms of a performance level when subjected to a specific test, or quite general. It may also contain potentially conflicting performance criteria that the formulator may need to redefine in the light of experience. Figure 1 shows a typical formulation process broken down into its constituent tasks and subtasks (1).

In designing a formulation, the formulator must take into account the properties of the active ingredient as well as possible chemical interactions between it and the other ingredients added to improve processibility and product properties since these may result in chemical instability. There may even be interactions between added ingredients, leading to physical instability. Commercial factors as well as the policy of the industry toward ingredient usage are important influences, as are production factors in the intended markets. The formulator may also routinely access databases on previous formulations as well as make use of mathematical models. During the formulation process, specific tests may need to be run to evaluate the properties of the proposed formulation and an analysis of zunexpected results may lead to an adjustment of the ingredients and/or their levels.

TECHNOLOGY

There is a wide divergence of views as to what defines an expert system. Examples include the following:

1. "An expert system is a knowledge-based system that emulates expert thought to solve significant problems in a particular domain of expertise" (2).
2. "An expert system is a computer program that draws on the knowledge of human experts captured in a knowledge base to solve problems that normally require human expertise" (3).

In its simplest form, an expert system has three major components: 1) an interface, a monitor, and keyboard that allow two-way communication between the user and the system; 2) a knowledge base where all the knowledge pertaining to the domain is stored; and 3) an inference engine where the knowledge is extracted and manipulated to solve the problem at hand. Inferencing strategies may be either forward chaining, which involves the system reasoning from data and information gained by consultation from the user to form a hypothesis, or backward chaining, which involves the system starting with a hypothesis and then attempting to find data and information to prove or disprove the hypothesis. Both strategies are included in most expert systems.

Knowledge in any domain takes the form of facts and heuristics; the former being valid, true, and justifiable by rigorous argument, the latter (often referred to as rules of thumb) being the expert's best judgment in any particular circumstance and hence justifiable only by example. Associated with these are the terms data and information, the former referring to facts and figures, the latter being data transferred by processing such that the data are meaningful to the person receiving the information. Knowledge can, therefore, be regarded as information combined with heuristics and rules. It is the objective of the knowledge engineer to acquire or elicit this knowledge and structure it in a computer-readable format.

Knowledge acquisition is probably one of the most difficult stages in the development of an expert system. It is both time-consuming and tedious as well as being expensive and often difficult to manage. However, it is a necessary element in the building of an expert system and, if done well, will undoubtedly lead to potentially useful systems. The basic model of knowledge acquisition is one of a team process whereby the knowledge engineer

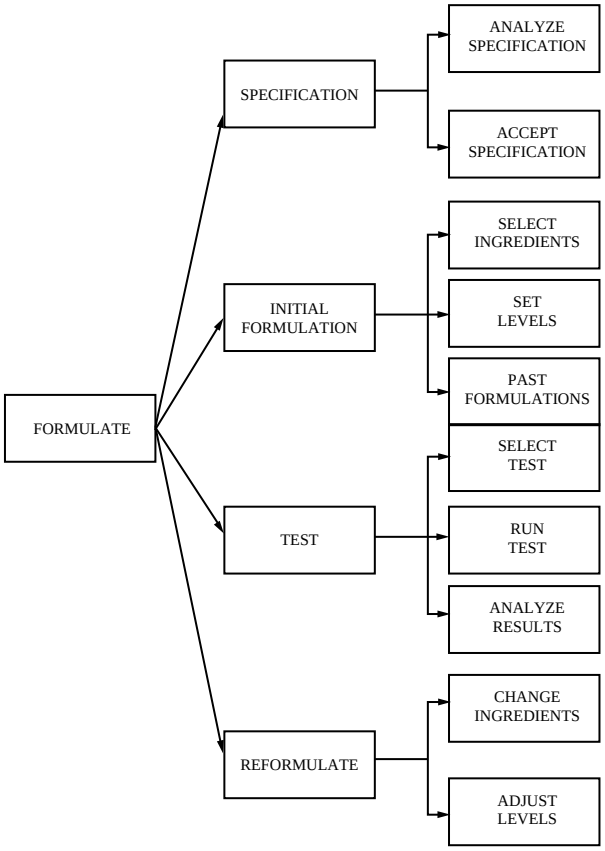

Fig. 1 Tasks and subtasks in the formulation process. (From Ref. 1.)

mediates between the expert(s), the users, and the knowledge bases. The knowledge engineer must acquire or elicit knowledge from not only the expert(s) but also from all the other potential sources, including written documents (research reports, reference manuals, and operating procedures policy statements) as well as consultants, users, and managers. In the case of experts, knowledge is usually acquired through face-to-face interviews. While this process is tedious and can place great demands on both the expert and knowledge engineer, it requires little equipment (e.g., tape recorder or notebook), is highly flexible, and often yields a considerable amount of useful information. At all times, there must be empathy between the participants and in many cases it is helpful to have two knowledgeable engineers present at the interview.

A technique that is often used in the acquisition process is the rapid prototyping approach. In this approach, the knowledge engineer builds a small prototype system as early as possible. This is then shown to both the expert and user, who can suggest modifications and additions. Here the system grows incrementally as more information and knowledge are gained. This methodology has been used successfully in the development of systems for the formulation of pharmaceuticals.

Once acquired, there are many ways of representing the knowledge in the knowledge base, including production rules, frames, semantic networks, decision tables, and trees and objects (2). Probably the most common methodology is the production rule, which expresses the relationship between several pieces of information by way of conditional statements that specify sections under certain sets of conditions, for example:

IF	(condition 1)
AND	(condition 2)
OR	(condition 3)
THEN	(action)
UNLESS	(exception)
BECAUSE	(reason)

Each rule implements an autonomous piece of knowledge and is easy to understand. Unfortunately, complex knowledge can require large numbers of rules, causing the system to become difficult to manage. The decision as to which method of knowledge representation should be adopted is dependent primarily on the complexity of the domain.

Expert systems can be developed using either conventional computer languages, special purpose languages, or with the assistance of development shells or tool-kits. Conventional languages such as PASCAL and C have the advantages of wide applicability and full flexibility to create the control and inferencing strategies required. They also are well supported and easy to customize. However, considerable amounts of time and effort are needed to create the basic facilities.

Specialized languages, such as LISP (a recursive language and the primary one for artificial intelligence research), PROLOG (a language based on first-order predicate logic), and SMALLTALK (an object-orientated language), have been used extensively in the development of expert systems. They have the advantages of applicability and flexibility of the conventional languages but are faster to implement.

Expert system shells and tool kits are sets of computer programs written in either conventional or specialized languages that can form an expert system when loaded with the relevant knowledge. They compromise on applicability and flexibility but allow more rapid development. Many offer basic facilities, including the means to prepare and store knowledge as a set of rules and to make deductions by chaining the rules together in an inferential process.

Shells differ in their secondary characteristics, such as user interfaces, operating speeds, the method of knowledge representation, and the associated algorithmic and arithmetic computational facilities. It is not surprising, therefore, that formulation is a highly specialized task that requires specific knowledge and often years of experience. This kind of expertise is not easily documented and hence, senior formulators often spend considerable amounts of time training new personnel. In addition, retirement or personnel moves can lead to a loss of irreplaceable commercial knowledge. Computer technology in the form of expert systems provides an affordable means of capturing this knowledge and expertise in a documented form available to all.

One such shell of specific importance in product formulation is Product Formulation Expert System (PFES), now termed Formulogic, developed by Logica UK Ltd. Formulogic a reusable software kernel and associated methodology to support the generic formulation process. It arose from research work during the mid-1980s and is now used for a variety of formulation support tools across a range of industry sectors, most notably pharmaceuticals (4, 5).

Formulogic is designed specifically for building formulation systems. Its formulation capability is generic, i.e., it is not specific to any particular domain. Individual formulation applications are developed using the shell by defining characteristics of the domain and the corresponding approach to formulation. The end result is a decision support tool for formulators that provides assistance in all aspects of the formulation development process. Formulogic provides the expert system developer with the knowledge representation structures that are common to most product formulation tasks so that a new application can be developed rapidly and efficiently. The architecture of Formulogic comprises three levels—the Physical Level, the Task Level, and the Control Level.

The Physical Level contains all the "nuts and bolts" of the formulation domain in a number of information sources, including a database. The Physical Level is accessed from the Task Level via a query interface. The physical net contains the domain knowledge in a number of objects. An object consists of a set of attributes, each of which may have zero or more values. The objects are arranged in a classification hierarchy. Subobjects, which descend from another object, inherit their attributes and values.

The Task Level is where the formulation problem-solving activity takes place. The formulation process is driven via the generation of a hierarchy of tasks. A task represents some well-defined activity. The hierarchy has an indefinite number of task levels. Domain knowledge about the formulation application is distributed throughout the hierarchy, with more abstract knowledge represented towards the top of the hierarchy and more specific knowledge toward the bottom.

The task decomposition allows the problem-solving process to be largely decoupled between tasks and also facilitates reasoning about subtasks. An important principle is that tasks plan about and directly manipulate only their immediate subtasks. Recursive application of this principle is the key to integrated behavior of a formulation system as a whole. The task tree is built on dynamically, depending upon the specification at hand as the problem-solving process proceeds. This is different to the object hierarchy where the structure is fixed for a particular domain.

Agendas, a particularly important class of objects used for communication between tasks, also are part of the Task Level. Agendas are important because the user exercises control over the formulation process principally through their manipulation. For parallel reasoning and backtracking by the user it is necessary to maintain more than one world. A world contains a formulation object and specification object together with agendas (in other words, a complete description of the state of the formulation process at any one time). Tasks run on a world or set of worlds; it is meaningless for tasks to run without reference to worlds.

Tasks perform their function by the execution of processes. Each task contains several types of processes. The precondition process assesses whether or not the task can play a sensible role in the current context. The action process performs the primary work of the task, which can include scheduling subtasks to be run next. The monitor process executes between each of the subtasks, typically to assess their result. Finally, the postcondition process assesses the success of the task as a whole immediately prior to completion.

Each process consists of a set of production rules; a rule is said to fire if its condition is true and its exception is false. When a rule fires, its action is executed. The reason is for information only and is not interpreted by Formulogic.

Rules are assigned a priority that reflects the order in which they should be considered. When executing a rule set, rules are tried in order until no more rules can fire. To find a suitable rule, Formulogic orders the rules first on priority and then on specificity. The first rule having a true condition and false exception is fired, and its action executed. The process of finding the next rule that can fire then starts all over again. To avoid looping, rules are only allowed to fire once with the same set of variable bindings.

The Control Level is concerned with the mechanics of running the Task Level. It contains no domain knowledge

and requires no design amendment when a new formulation system is built. Although the Task Level decides which tasks need running and the order in which they should run, the Control Level deals with the mechanics of actually running them and of passing control to them.

The typical functionality of a completed application is as follows:

1. The user enters the product specification, which forms the starting point of the formulation. In a tablet formulation, for example, this would consist of the drug details (unless already known to the system) and the dose.
2. Formulogic steps through a series of tasks to select ingredients and determine their quantities based on the product specification. It achieves this by following the rules and other knowledge that have been built into the system during development. An initial formulation is produced.
3. If the system performs reformulation in addition to producing initial formulations, then the user can enter the test results that have been performed on the product. Formulogic will then determine what kinds of problems with the formulation are indicated by the test results. The user can agree with the system's analysis of the problems or modify them as he or she sees fit. It uses the problem summary to make recommendations about what ingredients need to be added or what quantities need to be altered, and again the user can override the recommendations if he or she wishes. Once the user is happy with the recommendations, Formulogic will produce a modified formulation that meets the new requirements.

At any point during a session, the user can ask for an explanation of the results, browse the system's knowledge, or revert to an earlier stage of the process to modify the specification and obtain another formulation. The user can also save formulations (along with their associated product specifications) and generate printed reports.

APPLICATIONS

The first recorded reference to the use of expert systems in pharmaceutical product formulation was by Bradshaw on the April 27, 1989, in the London Financial Times (6), closely followed by an article in the autumn of the same year by Walko (7). Both refer to the work then being undertaken by personnel at ICI/Zeneca Pharmaceuticals (now AstraZeneca), United Kingdom (UK) and Logica UK Ltd. to develop expert systems for formulating pharmaceuticals using Formulogic. Since that time, several companies and academic institutions have reported on their experiences in this area (Table 1). This article will review these applications.

The Boots System

Although not strictly developed for pharmaceutical formulation, this system has been included since it is the only one known for formulating topicals. It was developed to assist formulators in the formulation of sun care products—a highly skilled occupation requiring 3–4 years of experience to attain a reasonable level of experience.

Implemented with the use of Formulogic, the system, called SOLTAN, uses knowledge captured by interviewing senior formulators. Ingredients, processes, and relationships of the formulation are represented in a way that reflects their groupings and associations in the real world. In addition, existing information sources, such as databases, are presented in a frame-based semantic network that can be manipulated by the problem-solving knowledge of the domain. Tasks are structured in a hierarchy that is built up dynamically depending on the specification at hand as the problem-solving process proceeds. Knowledge about the formulation is distributed throughout the task hierarchy, with strategic knowledge represented toward the top of the hierarchy and tactical knowledge towards the bottom.

The system was originally developed to formulate sun oils (solutions of ultraviolet absorbers in emollients) but has been rapidly extended, with the incorporation of basic emulsion technology, to cover oil-in-water lotions. Subsequently, the system has been further expanded to incorporate water-in-oil, oil-in-water, and water-in-silicone

Table 1 Published applications of product formulation expert systems in pharmaceuticals

Company/institution	Domain	Development tool
Boots Company	Topicals	Formulogic
Cadila Laboratories (India)	Tablets	PROLOG
University of Heidelberg	Aerosols Tablets Capsules Injections	C/SMALLTALK
University of London/ Capsugel	Capsules	C
Sanofi Research	Capsules	Formulogic
Zeneca Pharmaceuticals	Tablets Parenterals Film coatings	Formulogic

creams and lotions. It can now be used to formulate all types of skin care products, not just sun care products (8). The system won second prize in the UK DTI Manufacturing Intelligence Awards in 1991. It is the only system for which the developers have given details of costings and quantitative benefits.

The Cadila System

Cadila Laboratories Ltd. of Ahmedabad, India have developed an expert system for the formulation of tablets for active ingredients based on their physical, chemical, and biological properties (9). The system first identifies the desirable properties in the excipients for optimum compatibility with the active ingredient and then selects those that have the required properties based on the assumption that all tablet formulations comprise at least one binder, one disintegrant, and one lubricant. Other excipients such as diluents (fillers) or glidants are then added as required.

Knowledge is acquired through "active collaboration" with domain experts over a period of 6–7 months. It is structured in two knowledge bases in a spreadsheet format. In the knowledge base concerning the interactions between active ingredients and excipients, the columns represent the properties of the excipients with descriptors of "strong," "moderate," and "weak." The rows represent the properties of the active ingredients, e.g., functional groups (primary amines, secondary amines, highly acidic etc.), solubility (very soluble, freely soluble, soluble, sparingly soluble, slightly soluble, very slightly soluble, insoluble), density (low, moderate, high), etc. Each cell in the spreadsheet then represents the knowledge of the interaction between the various properties. Production rules derived from this knowledge are in the following forms:

IF	(functional group of active ingredient is "primary/secondary amine")
THEN	(add "strong" binder)
AND	(add "strong" disintegrant)
AND	(avoid lactose)

or

IF	(functional group of active ingredient is "highly acidic")
THEN	(add "moderate" binder)
AND	(add "moderate" disintegrant)
AND	(avoid starch)

or

IF	(active ingredient is soluble)
THEN	(add "weak" binder)
AND	(add "weak" disintegrant)

A similar approach is used for the knowledge base concerning the excipients, where the columns now represent details (e.g., name, minimum, maximum, and normal concentrations) of the excipients and the rows their properties (e.g., type and the descriptors—strong, moderate, and weak). Each cell in the spreadsheet then represents the name and the amount to be added to the formulation.

The system, written in PROLOG, is menu-driven and interactive with the user. The user is first prompted to input all the known properties of the new active ingredient. If the properties have descriptors, the user can select the appropriate ones. All information can be edited to correct errors. The expert system then consults the knowledge bases, suggesting compatible excipients and a formulation. If the latter is unacceptable, the system provides alternative formulations with explanations. All formulations can be stored along with explanations, if necessary. The user is able to update the knowledge base via an interface with a spreadsheet. An example of a formulation generated for the analgesic drug paracetamol, or acetaminophen, (dose 500 mg) is shown in Table 2. It is interesting to note that the diluent/filler is unnamed; it can be assumed that it will not be lactose since the relevant production rule indicates that there would be an interaction with the secondary amine in paracetamol. Furthermore, an examination of formulations on the market indicates that

Table 2 An example of a tablet formulation for the analgesic drug paracetamol as generated by the Cadila system

Input		
Dose	500 mg	
Functional group	Secondary amines	
Solubility	Sparingly soluble	
Density	Moderate	
Hygroscopicity	Moderate	
Dissolution	Slow	
Desired tablet weight	570 mg	
Output		
Active agent	Paracetamol	500.0 mg
Binder	Pregelatinized starch	43.7 mg
Disintegrant	Sodium starch glycolate	5.0 mg
Lubricant	Stearic acid	2.5 mg
Diluent/filler	Unnamed	20.0 mg
	Tablet weight	571.2 mg

(From Ref. 9.)

none contain lactose and that some contain mixtures of maize starch, sodium starch glycolate, stearic acid, magnesium stearate, and microcrystalline cellulose, adding further credibility to the Cadila system.

When first implemented, the prototype system had 150 rules, but this has expanded rapidly to approximately 300 rules in order to increase reliability. This is expected to increase further over time. The system is regarded as being highly successful, providing competitive advantage to the company (9).

The Galenical Development System

The Galenical Developmental System (GSH) was developed by personnel in the Department of Pharmaceutical and Biopharmaceutics and the Department of Medical Informatics at the University of Heidelberg, Germany. It is designed to provide assistance in the development of a range of formulations, starting from the chemical and physical properties of an active ingredient. The project was initiated in 1990 under the direction of Stricker (10), and in the interim has been extensively revised and enhanced (11, 12). Originally implemented using object-oriented C on a workstation, the system was recently upgraded using SMALLTALK V running under the Windows operating system on a personal computer.

Various forms of knowledge representation are used depending on the type of knowledge. Knowledge about objects (e.g., functional groups in the active ingredient, excipients, processes, etc.), their properties, and relationships are represented in frames using an object-oriented approach. Causal relationships are represented as rules, functional connections as formulas, and procedural knowledge as algorithms. The system currently has knowledge bases for aerosols, IV injection solutions, capsules (hard-shell powder), and tablets (direct compression). Each knowledge base incorporates information on all aspects of that dosage formulation (e.g., properties of the excipients to be added, compatibility, processing operations, packaging, and containers and storage conditions), with each aspect given a reliability factor (Sicherheitsfaktor) to indicate its accuracy/reliability. In the original version of the system values for each factor varied between 0 and 9 (10); however, values between 0 and 1 are used currently. The values are propagated using the arithmetic minimum rule and are not used for any decisions. They only serve as indicators of the accuracy/reliability of the knowledge.

The approach used in the system is the decomposition of the overall process into individual distinct development steps, with each step focusing on one problem associated with a subset of its specifications or constraints for the formulation. A problem is considered solved if its predicted outcome satisfies its associated constraints. The problems are worked through in succession, with care being taken that any solution should not violate any constraints from previous steps. For simplicity, the developers imposed a predefined ordering onto the development steps, providing a backtracking mechanism to go back to a previous step or abort. This ordering minimizes dependency between development steps, which might result in an action causing a constraint previously satisfied to be violated. It also reduces the complexity of the problem to be solved.

The procedural model for one development step (e.g., for the choice of an excipient) is shown in Fig. 2. In any development step the first decision is whether or not to proceed with any action since the problem may have already been solved in previous steps. This is done by comparing the predicted or relevant properties of the current formulation with the initial specification. If the answer is negative, then further action is required; if positive, the problem has been solved. Once this has been decided, actions need to be defined and ranked. Knowledge for this is by means of hierarchically structural rule sets to form a decision tree where each leaf node consists of a subgroup of actions and each branch a rule. The rules in a rule set are ordered as the simplest and most straightforward way of handling conflict. Ranking numbers are used as the basis for the selection strategy. The concept is to search for the best alternative in terms of the highest score, these being the sum of the values of the constants to be resolved within the development step (e.g., solubility, compressibility, etc.) and their weights indicating their respective importance (11, 12). It should be noted that this method of ranking is different from that used originally by Stricker et al. (10), where the lowest score was regarded as the best alternative.

Once the action is selected, the decision is checked in terms of whether or not the measure has adverse effects on the active ingredient in terms of physical or chemical incompatibility. This does not necessarily mean a rejection of the action since knowledge of compatibility is generally of a qualitative nature with little quantification to denote severity. Hence, the overall decision is left to the user.

The amounts of excipients to be used are calculated by formulae with rule-based mechanisms for selecting the appropriate formula. A rule-based mechanism is also used to determine the appropriate function for predicting the property of the intermediate formulation. This is necessary for checking whether or not the original specifications have been satisfied and the action is successful. If

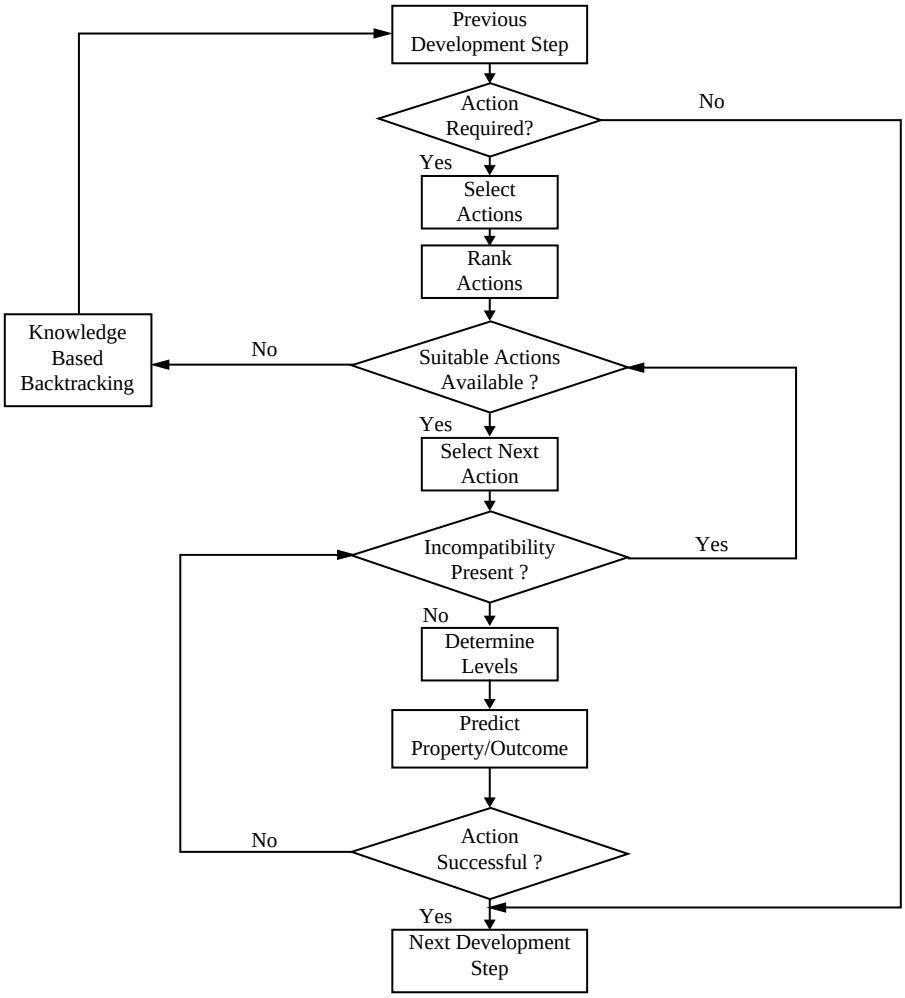

Fig. 2 Procedural model for a development step as used in GSH. (Modified after Ref. 12.)

negative, the chosen action is rejected and the next action in the ranking is tried. It is possible that none of the ranked actions is successful. If this is the case, then knowledge-based backtracking is used to determine which of the previous development steps to return to. Usually, background pharmaceutical knowledge is applied to determine why the current development step was unsuccessful, and a new development step that can solve the root cause of the problem is chosen.

In any expert system, explanations of the decisions made are important, both for instruction of the user and for maintenance of the system. Explanations in GSH take several forms. There are explanations for the development steps and their ordering provided by the designer of the knowledge base. Detailed explanations of the rules activated, formulae used, or individual scores of actions can be generated if required, and canned text and literature references are provided for general knowledge.

A simplified task structure for generating an iv injection solution is shown in Fig. 3. The input to the system includes all the known properties of the active ingredient to be formulated (e.g., solubility, stability, impurities, pK_a, presence/absence of functional groups, etc.) with user-defined labels that relate the specific drug property to the required product property. Use of the system results in the production of four packages—the product formulation, the production method, the recommended packaging and storage conditions, and predicted product properties. All the outputs are provided with reliability factors. An example for an IV injection solution of the cardiac drug digoxin is shown in Table 3, and an example for a hard gelatin capsule of the antifungal drug griseofulvin is shown in Table 4. Comparison of a 0.1 mg. commercial formulation of digoxin with that shown in Table 3 indicates that the same cosolvent is used (1,2-propandiol, presumably to enhance solubility) and ethanol. However,

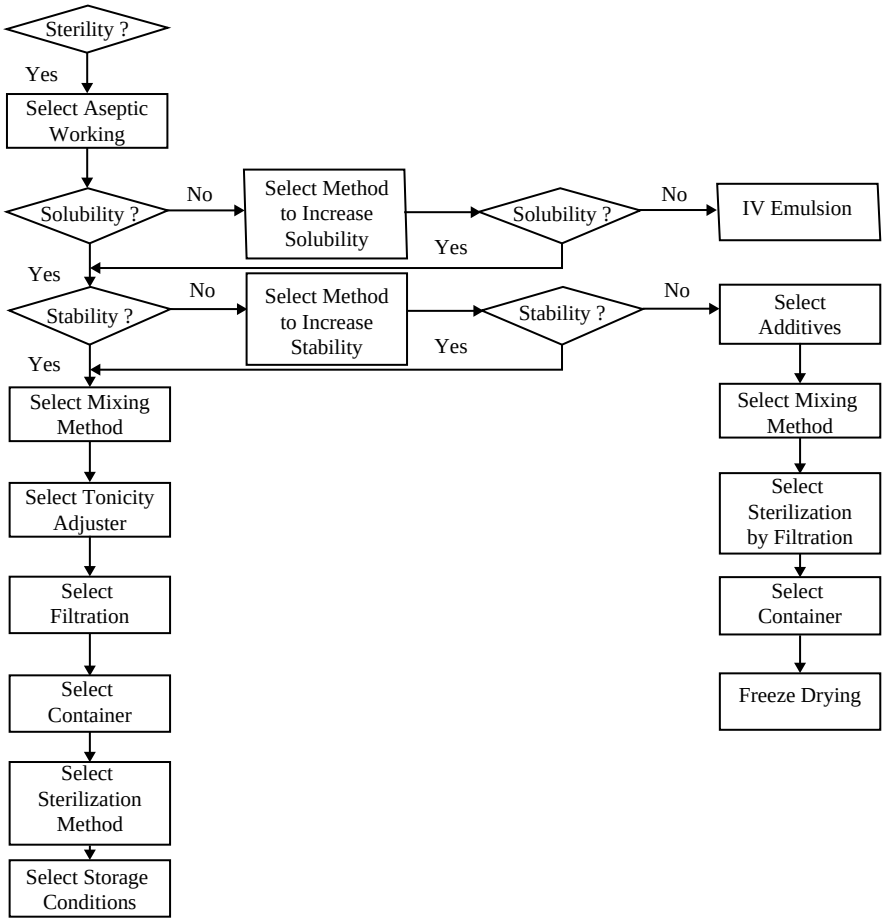

Fig. 3 Structure of the expert system described by Stricker et al. (10) for the formulation of intravenous injection solutions.

the commercial formulation is more sophisticated since it also contains a buffer (disodium hydrogen phosphate/citric acid).

At present, knowledge bases for aerosols, IV injection solutions, hard gelatin capsules, and direct compression tablets have been completed. Other knowledge bases for coated forms, granules, freeze-dried formulations, and pellets are in different stages of development. Trials have demonstrated that the system proposes formulations that are acceptable to formulators, and in December 1996, the system was first introduced for field trials in a pharmaceutical company.

The University of London/ Capsugel System

This system is designed to aid the formulation of hard gelatin capsules (13–15). It was developed as part of a Ph.D. program by Lai, Podczeck, and Newton at the School of Pharmacy, University of London, and was supported by Daumesnil of Capsugel, Switzerland, together with personnel from the University of Kyoto, Japan and the University of Maryland, United States. The system (Fig. 4) is unique in that its knowledge base is broad and contains the following:

1. A database of literature references associated with the formulation of hard gelatin capsules, which is permanently updated through monitoring of current literature.
2. Information on excipients used and their properties. This database currently contains information on 72 excipients and is frequently updated. Data can be retrieved via a menu.
3. An analysis of marketed formulations from Germany, Italy, Belgium, France, and the United States. This is used to identify trends in formulation and identify guidelines on the use of excipients. Currently, the database contains information on 750 formulations of 250 active ingredients. It is frequently updated and data can be retrieved via a menu.

Table 3 An example of an intravenous injection solution formulation for the cardiac drug digoxin as generated by GSH

Formulation		
Active	Digoxin	0.1 mg
Solvent 1	1,2-Propandiol	0.5 mL
	Water for injection to	1.0 mL
Packaging		
Brown glass ampules		
Product properties		

Properties	Specification	Actual	R.F.[a]
Active (mg)	0.095	0.098	1.0
Volume (mL)	1.0	1.0	1.0
pH	3–9	7.0	1.0
Freezing point depression (°C)	0.5–20	13.2	0.8
Shelf life at 25°C (years)		5.0	1.0
Decomposition at 25°C (mol)		1.8	0.7

[a]R.F., reliability factor.
(From Ref. 10.)

4. Experience and nonproprietary knowledge obtained over a period of 18 months from a group of industrial experts from Europe, the United States, and Japan.
5. Results from statistically designed experiments that identify factors that influence the filling and in vitro release performance of model active ingredients.

The system uses production rules with a decision tree implemented in C, coupled with a user interface through which the user can access both the databases and develop new formulations. To assist in collecting all necessary input data, a questionnaire has been designed. Called the expert system input package, it requires information on the physical properties of the active ingredient (e.g., dose, particle shape, particle size, solubility, wettability, adhesion to metal surfaces, melting point, and bulk density), compatibility of the active ingredient with excipients (e.g., fillers/diluents, disintegrants, lubricants, glidants, and surfactants), and properties of excipients used by the user and manufacturing conditions (e.g., capsule sizes, fill weights, densification techniques, granulation techniques) used by the user.

From this data the system uses a variety of methods to evaluate and predict properties of mixtures of the active ingredient and the excipients. For instance, it uses Carr's compressibility index (16) to predict the flow properties that are used to give an indication of the ability to produce a uniform blend, and the Kawakita equation (17) to predict a maximum in the volume reduction of the powder

Table 4 An example of a hard gelatin capsule formulation for the antifungal drug griseofulvin as generated by GSH

Formulation		
Active	Griseofulvin	150.0 mg
Diluent	Microcrystalline cellulose (PH102)	199.2 mg
Lubricant	Magnesium stearate	3.5 mg
Production process		
High shear mixer for deagglomeration, premix, and main mix.		
Add lubricant, planetary mixer at 12 rpm for 3 min.		
Capsule-filling machine type 1.		
Packaging		
Foil blisters (PVC and aluminum foil)		

(From Ref. 12.)

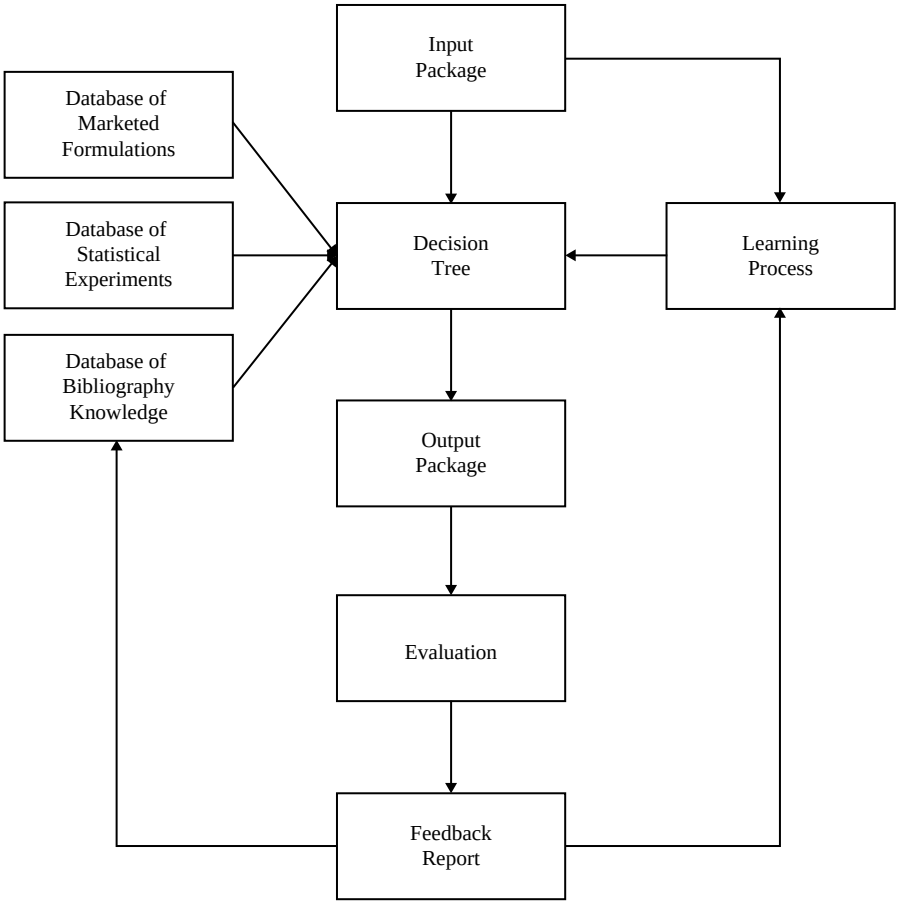

Fig. 4 Structure of the University of London/Capsugel system as described by Lai et al.

achievable by the application of low pressure. The packing properties are obviously important to give the volume that a given weight of powder occupies in order to indicate the size of capsule shell that can be used. When wet granulation is offered as the preferred method of densification, the system only offers advice on the choice of a granulating liquid and binder; no choice on the granulation procedure is offered.

The system provides an output package that includes a formulation (Table 5) with any necessary powder processing and filling conditions, the required capsule size, a statistical design to quantitatively optimize the formulation, specification of excipients used, recommended tests to validate the formulation, and a complete documentation of the decision process.

An interesting addition to the system is a semiautomatic learning tool. This monitors user habits and collects data about the use of excipients. Statistical analysis is performed on these data, allowing agreed alterations to be made to the database. The user is also asked to reply to a questionnaire regarding the recommended formulation and its performance. The data are analyzed by the expert system founder group, and provide the background for further alterations and developments.

Field trials have proved that the system does provide reasonable formulations (18).

The Sanofi System

Personnel at the Sanofi Research Division of Philadelphia recently developed an expert system for the formulation of hard gelatin capsules based on specific preformulation data of the active ingredient (19). Using Formulogic, the system generates one first-pass clinical capsule formulation with as many subsequent formulations as desired to accommodate an experimental design. The latter are produced as a result of the user overruling decisions made by the system.

Knowledge acquisition is obtained by meetings between formulators, with a knowledge engineer present as a

Table 5 An example of a hard gelatin capsule formulation for a model drug as generated by the university of londoncapsugel system

Tablet properties (*inputs*)			
Dose (mg)	50.0		
Solubility	Insoluble		
Particle size (μm)	5.0		
Minimum bulk density (g ml^{-1})	0.4		
Tapped bulk density (g ml^{-1})	0.7		
Carr's compressibility (%)	42.857		
Formulation			
		wt%	mg/capsule
Active	Drug	39.7	50.0
Filler	Starch:lactose (1:2)	56.8	71.6
Disintegrant	Croscarmellose sodium	2.0	2.5
Lubricant	Magnesium stearate	1.0	1.3
Surfactant	Sodium lauryl sulfate	0.5	0.6
Capsule weight			126.0
Capsule size			No. 4

(From Refs. 13 and 14.)

consultant. Meetings are limited to 2 h, with minutes being taken and reviewed by all attendees. Meetings are specific to one topic defined in advance. A rapid prototyping approach is used to generate the expert system.

Knowledge in the system is structured using the strategies implemented in Formulogic, i.e., objects and production rules. The latter are as follows:

Tasks are scheduled dynamically. An outline of the task structure used is given in Fig. 5.

IF	(electrostatic properties of a drug are problematic)
THEN	(add glidant)
UNLESS	(glidant has already been added)

The user is first prompted to enter specified preformulation data on the active ingredient (e.g., acid stability, molecular weight, wettability, density, particle size, hygoscopicity, melting point, solubility, etc.) and known excipient incompatibilities together with the required dose. At the initial formulation task, the capsule size is selected together with the process and milling requirements. The excipient classes are selected, with some excipients being excluded, others prioritized, and their amounts determined. At the display reports task, three reports are provided, one providing the preformulation data as given, the second giving the recommended formulation, including the amounts of the excipients and processing/milling requirements, and the third providing the explanation of the decisions and reasoning used by the system. On the first-pass through the system, the selection of the possible processing, milling, and excipient options are automatic. On subsequent passes, the selections are optional, allowing the user to generate a number of formulations.

An example of a formulation generated by this system, for the nonsteroidal anti-inflammatory drug naproxen, is given in Table 6. This example, as well as others, was considered acceptable by experienced formulators for manufacture and initial stability evaluation.

Unfortunately, the authors (19) do not provide any further details on the state of the system except to imply that formulation evaluation and preformulation tasks could be accommodated with the possible development for other formulation types such as tablets, liquids, and creams.

The Zeneca Systems

Work on expert systems within ICI/Zeneca Pharmaceuticals (now AstraZeneca) began in April 1988, with the initiation of a joint project between the Pharmaceutical and Corporate Management Services departments to investigate the use of knowledge-based techniques for the formulation of tablets. Since that time, work has proceeded with the successful development of expert systems for formulating tablets, parenterals, and tablet film coatings. All have been implemented using Formulogic from Logica UK Ltd., although elements of the system developed for

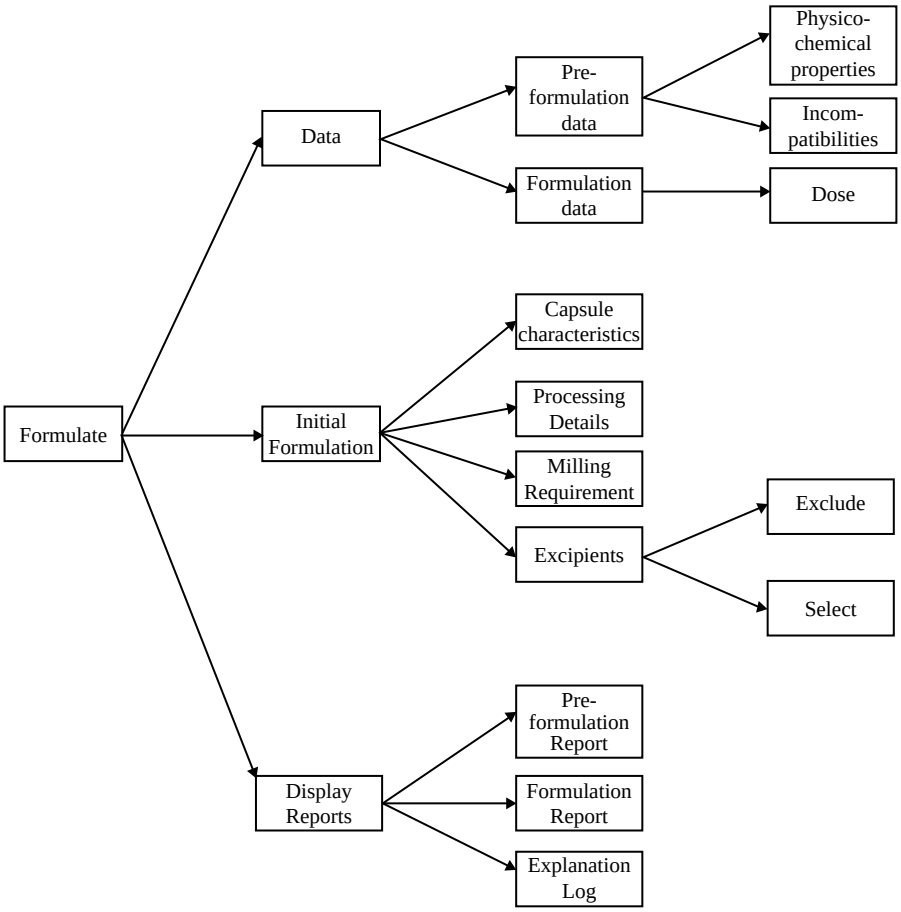

Fig. 5 Task structure for the formulation of hard gelatin capsules as used by Bateman et al. (19).

tablet film coatings were originally prototyped using a rule induction tool to produce decision trees.

Delivery of the first usable system for tablet formulation was in January 1989 (20, 21). All the knowledge was acquired from two primary experts in the field of tableting—one with extensive heuristic knowledge and the other with extensive research knowledge—and structured into Formulogic using specialist consultancy support. Consultancy time for the initial system was in the order of 30 man days, 20% of which was involved in three 2-day visits to the laboratories, incorporating three 90-min interviews with the experienced formulator plus members of the research group, the demonstration of prototype systems, and the validation of the previously acquired knowledge with the expert and other members of the department. Sixty percent of the time was involved in system development and 20% in writing the final report.

After commissioning and extensive demonstration to management and formulators throughout the company during 1989, the system was enhanced by the addition of a link to a database in January 1990, and the installation of a formulation optimization routine in September 1990. A major revision was initiated in February 1991, following a significant change in formulation practice. Total consultancy time for these enhancements was of the order of 30 man-days. In August 1991, the system was completed and handed over to the formulators both in the United Kingdom and the United States.

The completed system is shown in Fig. 6 (20). It is divided into three stages: 1) the entry of the data, product specification, and strategy; 2) the identification of the initial formulation; and 3) the formulation optimization as a result of testing the initial formulation. The sequence is as follows:

1. The user enters all the relevant physical, chemical, and mechanical properties (e.g., solubility, wettability, compatibility with excipients, and deformation behavior) of the new active ingredient to be formulated into the database. The data may be

Table 6 An example of a hard gelatin capsule formulation for the antiinflammatory drug naproxen as generated by the system described by Bateman et al.

Selected drug properties (inputs)		
Molecular weight		230.26
Melting point (°C)		155
Solubility in water (mg ml^{-1})		0.01
Wettability		Poor
Water stability		Poor
Photostability		Poor
Susceptible to hydrolysis		No
Primary/secondary amines		No
Hygroscopicity		Class 1
Poured density (g cm^{-3})		0.366
Electrostatic problems		No
Unmilled particle size (μm)		36
Formulation		
Active	Naproxen	100 mg
Diluent	Lactose (hydrous)	224 mg
Disintegrant	Microcrystalline cellulose (PH105)	60 mg
Surfactant	Sodium lauryl sulfate	4 mg
Lubricant	Talc	12 mg
Production information		
Milling	Jet milling of drug	
Capsule	Size 0 colored opaque	
Process	Direct blend	
Explanation log		
A colored opaque capsule used because drug is unstable to light.		
Drug requires milling as it has a medium particle size and is insoluble.		
A surfactant is required because drug has poor wettability.		

(From Ref. 19.)

numerical or symbolic (e.g., for solubility in water the data can be entered as mg ml^{-1} or as the descriptors "soluble," "partially soluble," "insoluble," etc. The data are obtained from a series of proprietary preformulation tests carried out on the active ingredient as received (i.e., 5 g of the drug milled to a specified particle size). These tests include excipient compatibility studies whereby the drug is mixed with the excipient and stored under specified conditions of temperature and humidity for one week, the proportion of drug remaining being analyzed by HPLC and expressed as a percentage. The deformation properties essential for the evaluation of compactibility are assessed using yield pressure and strain rate sensitivity measured via a compression simulator (22).

2. The user enters the proposed dose of the active ingredient and a target tablet weight is calculated using both a formula determined from an extensive study of previously successful formulations and certain rules governing minimum weights for ease of handling and maximum weights for ease of swallowing.
3. The user selects a strategy dependent on the number of fillers (one or two).
4. The system selects the filler(s), disintegrant, binder, surfactant, glidant, and lubricant, and their recommended concentrations based on a combination of algorithms, formulae, and mixture rules governing their compatibility and functionality. Tasks in this process are dynamically scheduled depending on the problem to be solved. If the system is unable to decide between two excipients, both of which satisfy all the embedded rules, then the user is asked to select a preference.
5. The recommended initial formulation is displayed, including final tablet weight, recommended tablet diameter calculated compression properties, and all relevant data (Table 7). This is normally printed for inclusion in a laboratory notebook, file, etc. If required,

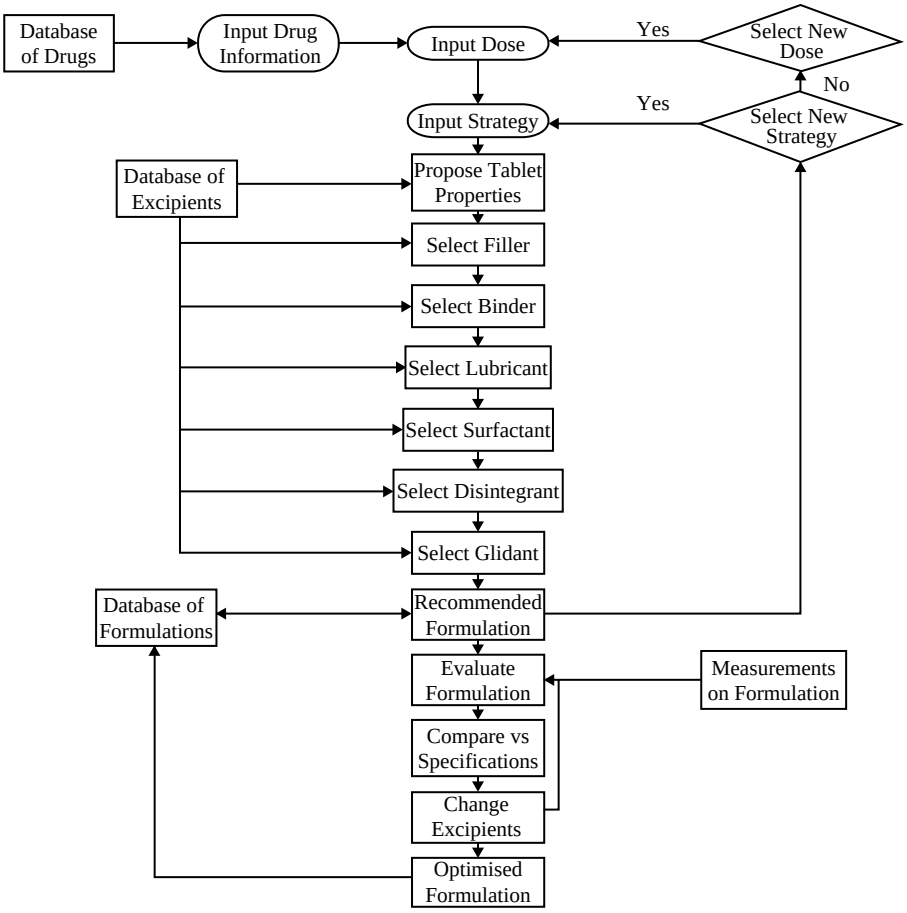

Fig. 6 Structure of the expert system developed by Rowe (20) for the formulation of tablets.

the data may be stored in a database for future reference, necessary if the formulation optimization route is used.

6. The user enters results from testing tablets prepared using the initial formulation. These may include disintegration time, tablet strength, tablet weight variation, and presence of any defects (e.g., capping, lamination, etc.). The results are compared with specifications, and any problems identified are confirmed with the user. Recommendations for modifications to the formulation are then listed. This routine is fully interactive with the user, who is asked to confirm or contradict/change the advice given.
7. After agreement is reached, the system modifies the formulation accordingly and displays it as described earlier. This routine may be used as many times as required; each time, the system iterates on the previously modified formulation.

Two "help" routines are embedded in the system, one to provide on-line help in the use of the system, the other to provide an insight into the rationale behind adoption of the specific rules/formulae/algorithms used. The user is able to browse the knowledge base at will but is not able to edit it without privileged access. Explanations for any recommendations made by the system can be easily accessed, if required. Hypertext links are used throughout. Two screen images from the system are shown in Fig. 7 to illustrate the operation of the system.

The system is well used and is now an integral part of the development strategy for tablet formulation. To date, it has successfully generated formulations for more than 40 active drugs. In many cases, the initial formulations have been acknowledged as being on a par with those developed by expert formulators. Consequently, the formulation optimization routine is now considered redundant and is used very rarely.

Following the successful implementation of the tablet formulation expert system, a request was made for the development of a similar system for parenteral formulations. This project was initiated in April 1992, and

Table 7 Examples of tablet formulations for a model drug as generated by the system described by Rowe

Drug properties (inputs)	
Solubility (mg ml^{-1})	0.1
Contact angle	82°
Yield pressure (MPa)	50
Strain rate sensitivity (%)	50
+ Excipient compatibilities	

Formulation

		Quantity (mg)	Quantity (mg)
Active	Drug A	50.0	150.0
Filler	Lactose monohydrate	166.9	–
Filler	Dicalcium phosphate dihydrate	–	165.7
Disintegrant	Croscarmellose sodium	4.8	7.0
Binder	Polyvinylpyrrolidone	4.8	–
Binder	Hydroxypropylmethyl cellulose	–	7.0
Surfactant	Sodium lauryl sulfate	0.7	1.1
Lubricant	Magnesium stearate	2.4	3.5
Tablet weight		230.0	335.0

	Predicted properties	Formulation
	50 mg	150 mg
Tablet diameter (mm)	8.0	10.0
Yield pressure (MPa)	139	238
Strain rate sensitivity (%)	20.8	5.1

(From Ref. 20.)

completed in August 1992 (23). The structure of the system is shown in Fig. 8. It is designed for formulating a parenteral for either clinical or toxicological studies in a variety of species (dog, man, mouse, primate, rabbit, or rat) by a variety of routes of administration (iv, intramuscular, subcutaneous, interperitoneal), supplied in either a single or multidose container. Knowledge was acquired from two domain experts using a series of interviews. The sequence is as follows:

1. The user enters all known data on the solubility (aqueous and nonaqueous), stability in specified solutions, compatibility, pK_a, and molecular properties of the active ingredient (molecular weight, log P, etc.). As with the system for tablet formulation, the data may be numerical or symbolic. All relevant properties of additives used in parenteral formulation (e.g., buffers, antioxidants, chelating agents, antimicrobials, and tonicity adjusters) are present in the knowledge base.
2. The selection first attempts to optimize the solubility/stability of the active drug at a range of pH using a variety of formulae and algorithms together with specific rules before selecting a buffer to achieve that pH. If problems still exist with solubility and stability, then formulation variants (e.g., oil-based or emulsion formulations—not implemented in the present system) are recommended.
3. The system then selects additives, depending on the specification required (e.g., an antimicrobial will only be added if a multidose container is specified or a tonicity adjuster will only be added if the solution is hypotonic). The selection strategy is generally on the basis of ranking with some specific rules.
4. The recommended formulation is displayed with all concentrations of the chosen ingredients expressed as percentage weight by volume (w/v) together with the calculated tonicity, proposed storage conditions, and predicted shelf life (Table 8). Specific observations on the sensitivity of the formulation to metals, hydrolysis, light, and oxygen also are included. This is normally printed for inclusion in a laboratory notebook, file, etc. If required, the formulation may be stored in a database for future reference.

As with the system developed for tablet formulations, this system contains extensive "Help" routines. No

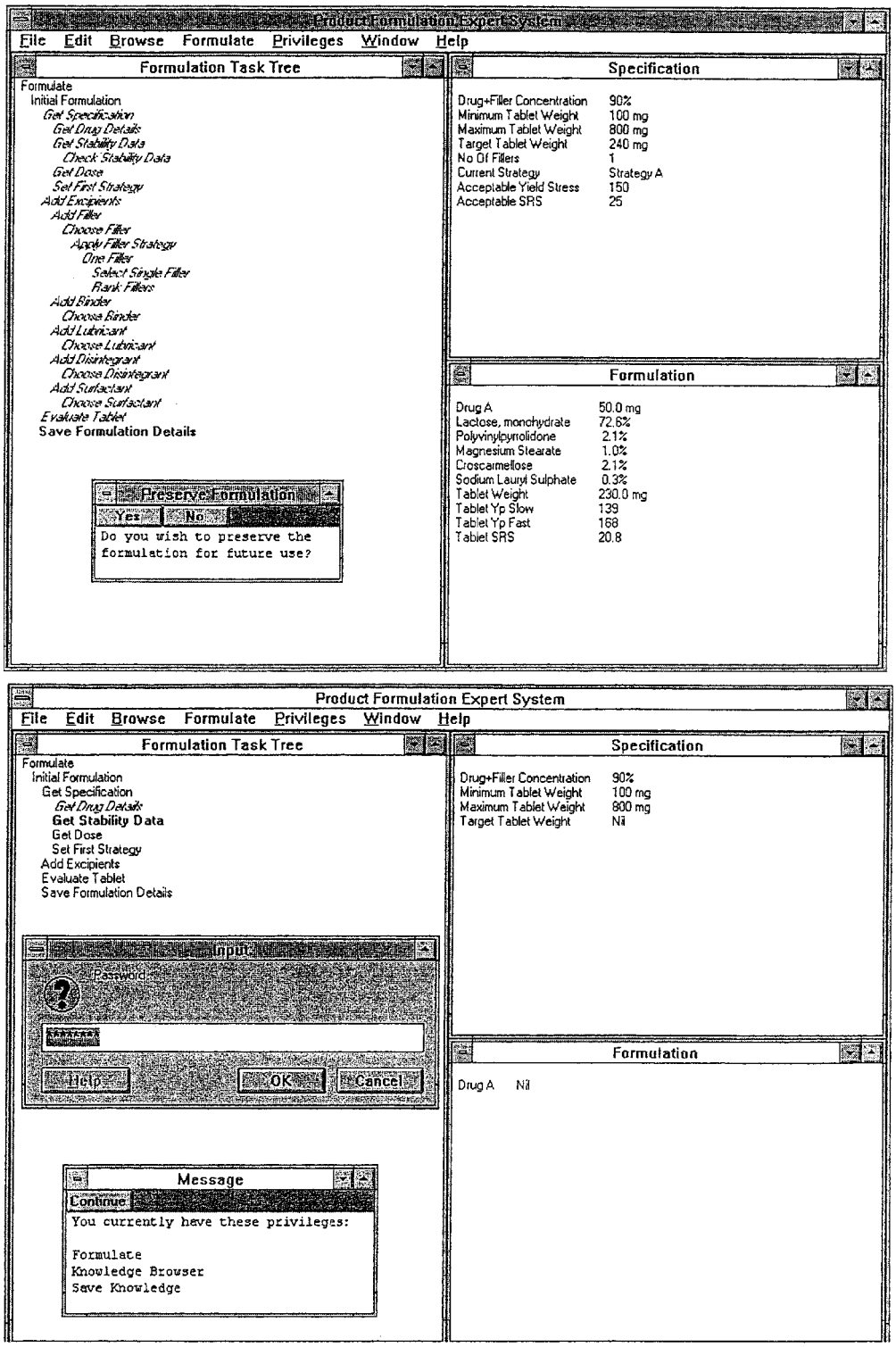

Fig. 7 Screen images for the tablet formulation expert system as described by Rowe (20). (a) Shows user interface with windows for the formulation task tree, specification, formulation, and current task. Tasks are displayed in various formats—current task in highlighted or bold text, completed in italics, and future in standard text. (b) Shows the security of the system. The input of a password displays the user privileges.

Table 8 An example of a formulation of an intravenous injection for clinical trials in man as generated by the system described by Rowe et al.

Drug properties (inputs)		
Drug type		Acid
pK_a		4.5, 3.5
Molecular weight		458.5
Solubility (mg ml^{-1})	pH 3.0	0.5
	pH 4.0	1.5
	pH 5.0	7.0
	pH 7.0	40.0
Sensitivity	Light, metal, oxygen	
Formulation		Quantity (% w/v)
Active	Drug (10 mg/ml)	1.00
Buffer	Disodium hydrogen phosphate anhydrous	0.87
Buffer	Hydrochloric acid	q.s.
Chelating agent	Disodium edetate	0.02
	Water for injection to	100.00
Predicted solution properties		
pH	7.4	
Tonicity	Hypertonic (1.6)	
Storage temperature (°C)	25	
Atmosphere for filling	Nitrogen	
Shelf life (years)	>5	

(From Ref. 23.)

formulation optimization routines are included, although a routine to develop a placebo formulation to match the active formulation is included. The system is used to recommend parenteral formulations for a wide range of investigational drugs.

Work on expert systems in the specific domain of tablet film coating was initiated in April 1990, using a rule induction tool in order to develop a system for the identification and solution of defects in film-coated tablets. Although not strictly a formulation expert system, the developed system did contain knowledge whereby a given formulation known to cause defects could be modified to provide a solution. The completed system described by Rowe and Upjohn (24, 25) is a perfect illustration of fault diagnosis with a rule-based decision tree including both forward and backward chaining. Total development time was approximately 1 man-month using both documented knowledge (26) and expert assistance.

The system (Fig. 9) is divided into three parts: identification, solution, and information/references. In the first part, a question and answer routine is used to ascertain the correct identification of the defect. The decision tree used for this process is shown in Fig. 10. At this point, the user is asked to confirm the decision by comparing the defect with a picture or photographs stored in the database. In the second part, the user is asked to enter all relevant process conditions and formulation details regarding the best way of solving the defect. This may be a change in the process conditions, as in the case of defects occurring with an already registered formulation, or a change in the formulation, as in the case of defects occurring at the formulation development stage. In the third part, the user is able to access data and knowledge regarding each defect. These are in the form of notes, photographs, and literature references connected by hypertext links.

In 1994, due to the successful implementation of both this system and that used to formulate tablets, it was decided to initiate work on a new system that would recommend film-coating formulations for the generated tablet formulations, combined with a reformulation routine based on the film defect diagnosis system (27). The structure of the new system is shown in Fig. 11. The knowledge for the system was acquired by interviewing two domain experts, one with extensive heuristic knowledge and the other with extensive research knowledge. The sequence is as follows:unital)

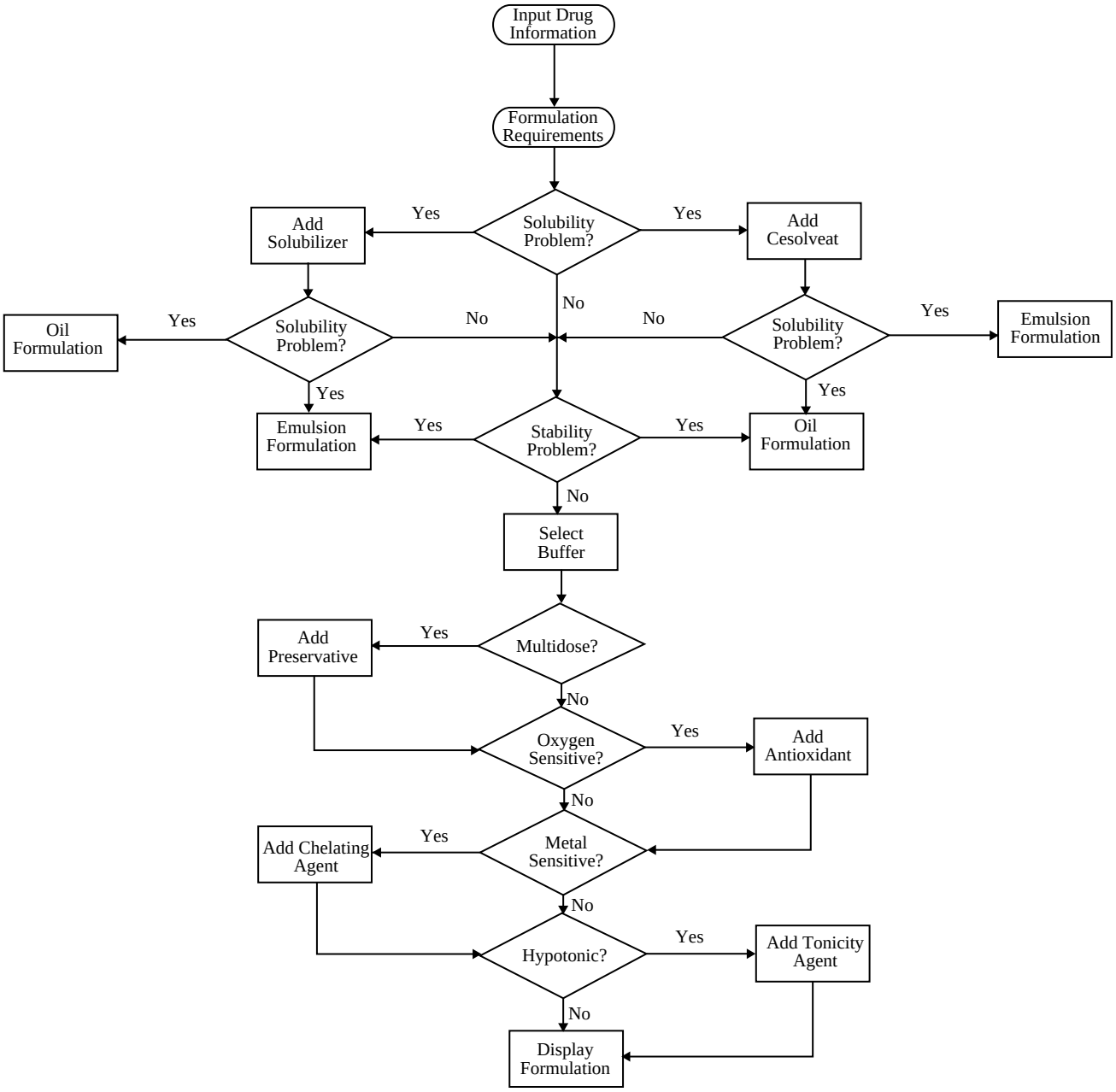

Fig. 8 Structure of the expert system developed by Rowe et al. (23) for the formulation of parenterals.

1. The user enters details of the tablet formulation (e.g.,dose of active ingredient and all excipients) together with all tablet properties (e.g., diameter, thickness, strength, friability, color, shape, and the presence/ absence of intagliations).
2. The user enters specifications for the film coating formulation (i.e., immediate release/controlled release, enterosoluble, white or colored).
3. The system first checks that there are no inconsistencies between the input details and the required specification (e.g., tablets with high friabilities are extremely difficult to film coat). If positive, a warning is displayed.
4. The system calculates the surface area of the tablet and selects the required polymer at the recommended level to form a film of reasonable thickness.

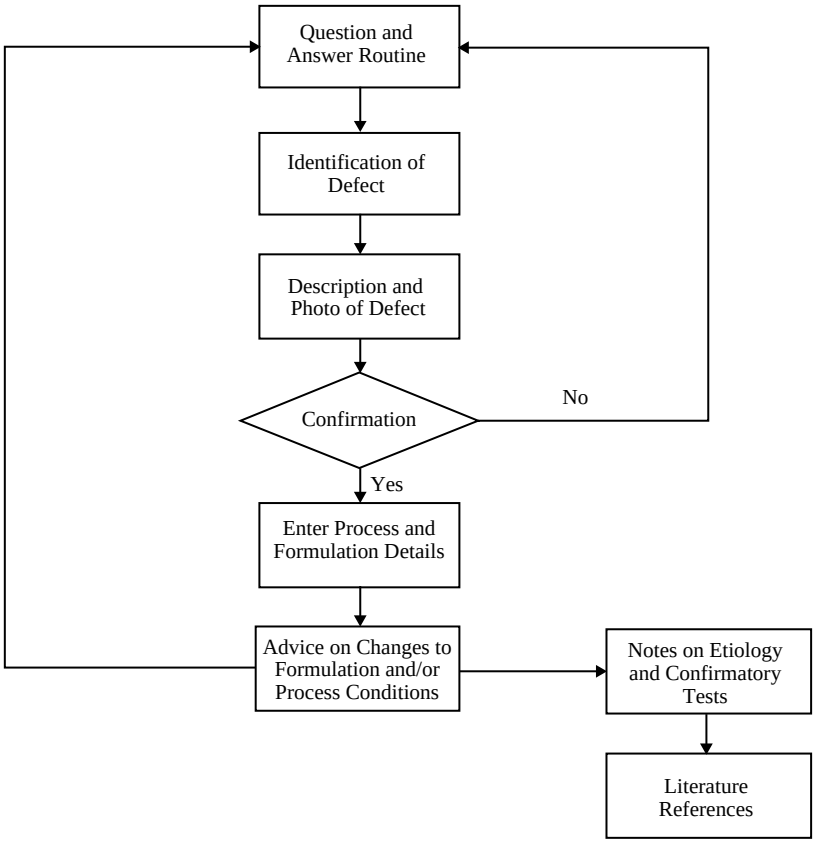

Fig. 9 Structure of the expert system for the identification and solution of film coating defects as described by Rowe and Upjohn (24, 25).

Table 9 An example of a formulation of a white film coating for a tablet of a model drug as generated by the system described by Rowe et al.

Tablet properties (inputs)		
Tablet core formulation	Drug A 50 mg	
Punch shape	Normal concave	
Weight (mg)	230	
Diameter (mm)	8.0	
Thickness (mm)	3.5	
Surface area (cm^2)	1.49	
Formulation	mg/tab	mg/cm^2
Polymer Hydroxypropyl methylcellulose (6 cps)	6.14	4.12
Plasticizer Polyethylene glycol (PEG 400)	1.23	0.82
Pigment Titanium dioxide (Anatase)	5.63	3.78
Predicted film properties		
Thickness (μm)	45	
Opacity (%)	94.9	
Crack velocity (ms^{-1})	5.71	

(From Ref. 27.)

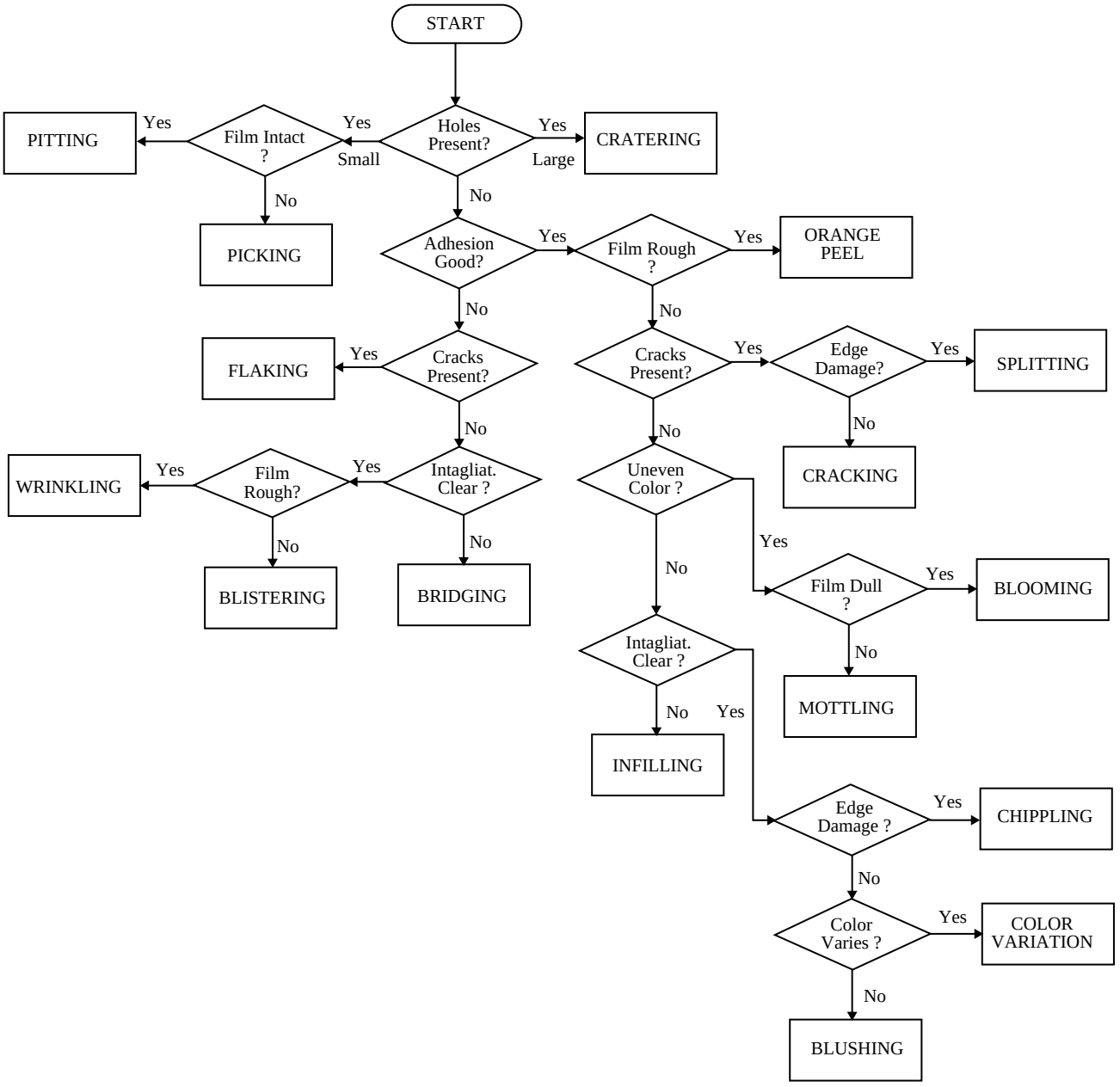

Fig. 10 A decision tree for the identification of film defects on film-coated tablets. (From Ref. 25).

5. The system selects a plasticizer and checks that there are no stability/compatibility problems. If positive, the user is asked to select an alternative plasticizer.
6. The system defines the target opacity of the film coating and decides if an opaque coating is required. The opacity is assessed by means of the contrast ratio defined as the ratio of the reflectance of the film when viewed with a black background to that viewed with a white background (the higher the value the more opaque the film) (28, 29). If positive and the specification has been set as white, the system uses specifically developed algorithms (30, 31) to calculate if the target specification can be achieved within certain predefined formulation limits of the volume concentration of titanium dioxide and film thickness. If negative, the user is provided with a series of options to continue with the predefined limits, change the limits, or select a colored film coating.
7. The system selects the pigments to achieve the target specification and determines the amount of water

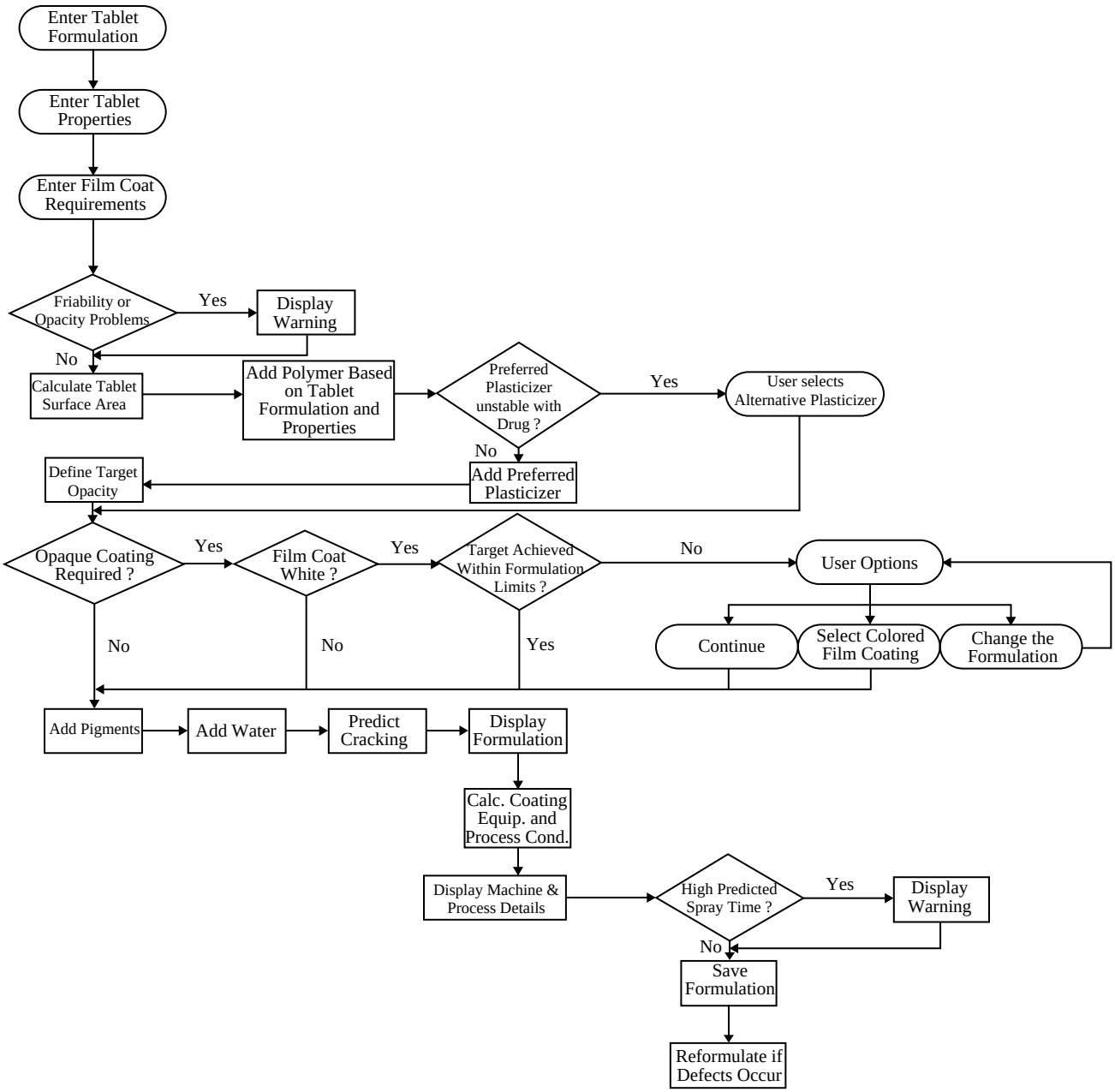

Fig. 11 Structure of the expert system developed by Rowe et al. (27) for the formulation of tablet film coatings.

(the system has been developed for aqueous film coating only).

8. The system accesses a simulation program written in C to predict the cracking propensity of the film formulation (32–34).
9. The recommended formulation is displayed (Table 9) and includes predicted film thickness, opacity, and cracking propensity. Standard machine settings and process details also are displayed with warnings if the total spray time is judged to be excessive. This is normally printed for inclusion in a laboratory notebook or file. If required and in particular if reformulation is likely to be necessary, the data may be stored in a database for future reference.
10. If a reformulation is necessary due to the presence of defects after coating, then the system uses a modified form of the defect diagnosis system to recommend changes in the formulation and/or process conditions.

This system has proved successful in initial trials, especially in the formulation of opaque films for drugs that are either unstable to light or colored, producing mottled tablets. The calculations concerning the achievement of the target opacity within predefined limits have enabled formulators to make informed decisions regarding the use of white or colored film coatings. The system is now an integral part of the development strategy for film-coated tablets and now has a common database with the tablet formulation system.

BENEFITS

Expert systems have many benefits. These include the following:

1. *Knowledge protection and availability*. The existence of a coherent, durable knowledge base not affected by staff turnover (20). The developers of the University of London/Capsugel system have reported the benefit of being able to use knowledge from experts from many industrial companies in Europe, the United States, and Japan (14, 15). The developers of both the Cadila and the Sanofi systems have reported the benefit of the prompt availability of information and the rapid access to physical chemical data of both drugs and excipients, reducing the time spent searching the literature (9, 19).
2. *Consistency.* All systems generate robust formulations with increased certainty and consistency. This is seen as a distinct benefit where regulatory issues are important.
3. *Training aid.* All systems have been used to provide training for both novice and experienced formulators. The developers of the SOLTAN system have stated that experienced formulators use their expert systems to expose themselves to new raw material combinations with which they are not familiar. Bateman et al. (19) suggested the documentation used in the development of the Sanofi system be adapted to train novice formulators.
4. *Speed of development.* Reduction in the duration of the formulation process has been reported by many (8, 9, 20). Wood (8) reported that formulators who use SOLTAN can produce a formulation in 20 min that might otherwise have taken 2 days. Ramani et al. (9) reported a 35% reduction in the total time needed to develop a new tablet formulation.
5. *Cost savings.* Cost savings can be achieved not only by reducing the development time but also by the more effective use of materials, especially if material cost and controls are included in the system. Ramani et al. (9) reported that use of their system has been a benefit in planning the purchase and stocking of excipients. The developers of SOLTAN reported that formulations generated by their system are cost effective not only for savings in raw material costs but also because fewer numbers of ingredients are used as compared to traditional formulations. Several users have also reported a decrease in the size of raw material inventories since their expert systems only use those materials specified in the database.
6. *Freeing experts.* The implementation of expert systems in product formulation has inevitably allowed expert formulators to devote more time to innovation (8, 20). The developers of the SOLTAN system reported that the time saved using their expert system typically releases about 30 days of formulating time per year per formulator. Of course, experienced formulators originally involved in training also will have more time to devote to innovation.
7. *Improved communication.* Rowe (20) reported that expert systems in his company have provided a common platform from which to discuss and manage changes in working practice and to identify those critical areas requiring research and/orrationalization. The developers of SOLTAN reported that use of their system has made them scrutinize the way in which they formulated products, highlighting shortfalls from the ideal. They also report that they have discovered previously unknown relationships between ingredients and properties in their products. The benefit of an expert system in promoting discussion also was reported by Bateman et al. (19).

Of all the systems in product formulation, only one has provided costings and undertaken a cost benefit analysis. The developers of SOLTAN estimated the overall cost of their system to be £10,400 for hardware and software, £6000 for consultancy, and £9000 for expert's time, making a total of £25,400. Annual cost savings in the region of £200,000 were reported, delivering a payback of approximately 3 months.

It is interesting to note that where expert systems have been implemented in product formulation, early skepticism among potential users has generally changed to a mood of enthusiastic participation. It is unlikely that expert systems will ever replace expert formulators, but as a decision support tool they are invaluable, delivering many measurable and intangible benefits.

CONCLUSION

Expert systems have been developed by a number of pharmaceutical companies and academic institutes in

order to cover the most common formulation types. Only those that have been mentioned in the open literature have been discussed, although it is generally known that SmithKline Beecham, Glaxo Wellcome, Eli Lilly, and Pfizer also have developed systems. It is possible that many more systems exist, but reticence with regard to publication abounds, and it is difficult to estimate exactly the number developed.

ACKNOWLEDGMENTS

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